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BLANK ROME LLP ONE LOGAN SQUARE PHILADELPHIA, PA 19103			EXAMINER POLANSKY, GREGG	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/569,863

Applicant(s)

HOLM ET AL.

Examiner

GREGG POLANSKY

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Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 August 2010 and 19 October 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3-10, 16-20, 22-29, 31-34, 36-44 and 51-57 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3-10, 16-20, 22-29, 31-34, 36-44 and 51-57 is/are rejected.
- 7) ☒ Claim(s) 38 and 39 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-502)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 8/12/10 & 12/14/10
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Status of Claims

1. By way of the submission filed on 8/12/2010, Applicants have canceled Claim 21, amended Claims 1, 3-5, 16, 22, 23 and 56, and presented arguments in response to the Office action mailed 3/31/2010.
2. Applicants' Information Disclosure Statements, filed 8/12/2010 and 12/14/2010, are acknowledged and have been reviewed.
3. Claims 1, 3-10, 16-20, 22-29, 31-34, 36-44 and 51-57 are pending and presently under consideration.
4. Applicants' arguments have been fully considered and are persuasive in part. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Inventorship

5. In view of the papers filed 10/19/2010, the inventorship in this nonprovisional application has been changed by the deletion of Tomas Norling.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

Response to Amendment

6. The Declaration under 37 CFR 1.132 filed 8/12/2010 is sufficient to overcome the rejection of Claims 1, 3-10, 16-29, 31-34, 36-44 and 51-57 under 35 U.S.C. 103(a) as being unpatentable over Holm et al. (WO 03/004001 A1), in view of "Tacrolimus (Systemic)" (Drugs.com).

Claim Objections

7. The Claims submitted by Applicants on 8/12/2010 improperly identifies Claims 38 and 39 as "Withdrawn". Claims 38 and 39 should be labeled as "Previously Presented".

Terminal Disclaimer

8. The terminal disclaimer filed on 8/12/2010 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of any patent granted on application #10/569,862 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 6, 7, 36, 37 and 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6 and 7 recite the limitation "the vehicle". There is insufficient antecedent basis for this limitation in the claim. The "vehicle" is not defined by the claims or parent Claim 1.

Regarding Claim 36, the phrase "substituted and/or unsubstituted diglycerides" and "substituted and/or unsubstituted triglycerides" renders the claim indefinite because it fails to define the invention properly by not specifically defining the substituents.

Claim 44 recites the limitation "the active ingredient" in line 3 of the claim. There is insufficient antecedent basis for this limitation in the claim. The "active ingredient" is not defined by the claim or from claim from which it depends.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

12. Claims 1, 3-10, 16-20, 22-26, 31-34, 36-44 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koretke et al. (WO 01/95939 A1; previously cited), in view of Kelm et al. (WO 93/23022; cited by Applicant on IDS filed 12/09/2009) and "Tacrolimus (Systemic)" (Drugs.com; previously cited; hereinafter referred to as "Drugs.com"), as evidenced by Yang et al. (International Journal of Pharmaceutics, 1992, Vol. 86(2-3) pp. 247-257, Abstract only; previously cited) and Kjaergaard et al.

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("Prilling – Multiple Core Encapsulation", GEA Process Engineering, Inc., GEA-Niro A/S R1, 8/2000, pages 1-10 of 10).

Koretke et al. teach a fast release solid dispersion pharmaceutical composition of an active compound, poloxamer 188 and polyethylene glycol having a molecular weight of 6000 (PEG 6000). See Abstract and pages 9-10, claims 1, 8, and 9-11. The compositions taught by Koretke et al. can be formulated as capsules. Whereas the capsules are made by filling capsules with the composition in the form of a melt, the empty (gelatin) capsule serves as a solid carrier. See page 7, lines 19-24. The ratio of polyethylene glycol to poloxamer taught by Koretke et al. is in the range of 3:1 to 49:1. Koretke et al. teach solid dispersion compositions comprising about 0.1% to about 20% active agent. See page 9, claim 4. The reference teaches the disclosed fast release solid dispersion composition increases the bioavailability of water insoluble drugs without the need for using organic solvents. See page 2, lines 20-22. Solid dispersion formulations comprise a drug dissolved or dispersed in a polymer. See page 1, lines 1-2. Thus, the solid dispersion compositions taught by Koretke et al. comprise an active ingredient in the form of a solid dispersion and/or a solid solution with the composition polymer(s). The poloxamer and polyethylene glycol of the composition are pharmaceutically acceptable excipients. The compositions of Koretke et al. are suitable for oral administration. See page 10, claim 12. Polyethylene glycol is a polyether glycol (a hydrophilic oily material), thus satisfying the requirements of instant Claims 33 and 34. The reference teaches additional agents may be added to the composition. These agents include, for example, various cellulosic polymers, acacia, sodium alginate, and

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starch. See page 6, lines 9-24. These agents can act as, for example, suspending agents, flavoring agents, release modifying agents, and stabilizing agents. Koretke et al. teach the use of aminoalkyl methacrylate copolymer E (i.e., EUDRAGIT E) as a "gastric coating base" (i.e., release modifying agent). Hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, cellulose acetate phthalate, methacrylic copolymer LD and S and ethylcellulose (as required by instant Claim 32) are also taught by the reference. See page 6, lines 9-24. The use of, *inter alia*, ethylcellulose as an enteric coating agent (i.e., release modifying agent) is well known in the art. For example, see Yang et al. (International Journal of Pharmaceutics, 1992, Vol. 86(2-3) pp. 247-257, Abstract only; provided previously for evidentiary purposes only).

Poloxamer 188 in the formulation of Koretke et al. (*supra*) satisfies the requirement of instant Claim 38 (i.e., a poloxamers). EUDRAGIT E and other methacrylic polymers (*supra*) satisfy the requirements of instant Claims 38 and 39.

The limitations of Claims 40 and 41 are met by at least Koretke et al. teaching aminoalkyl methacrylate copolymer E as a gastric coating and hydroxypropylmethylcellulose acetate succinate, cellulose acetate phthalate, methacrylic copolymer LD and S (*supra*), all of which are known to be used as pharmaceutical coating agents (the water solubility of each agent is pH-dependent as instantly disclosed).

Koretke et al. teach compositions useful for increasing the bioavailability of water insoluble drugs. The reference, does not specifically teach compositions comprising tacrolimus.

Drugs.com teaches tacrolimus being practically insoluble in water, and that tacrolimus has "[r]apid, variable, and incomplete [absorption] from the gastrointestinal tract" and a mean oral bioavailability of 27%, with a range of 5-65%. See Solubility, at page 2 and Absorption at page 3.

The need for a tacrolimus composition having improved bioavailability would have been obvious to one of ordinary skill in the art at the time of the invention because Drugs.com teaches the poor bioavailability of tacrolimus. Since Koretke et al. teach compositions useful for increasing the bioavailability of water insoluble drugs it would have been obvious to the artisan to utilize the methods of Koretke et al. to produce a more bioavailable tacrolimus composition with a reasonable expectation of success.

Kelm et al. teach solid dispersions in the form of a solidified melt mixture comprising a water insoluble drug (tebufelone), a poloxamer surfactant (e.g., poloxamer 188) and polyethylene glycol having a molecular weight of 1500 or greater. See page 9, claims 1, 2, 4 and 5. Kelm et al. disclose the disclosed compositions (i.e., solid dispersions) "can be formed into flowable particles by suitable means...[such as] oscillating screen sized reduction of solidified melt mixtures and prilling of the melt." The particles are formulated into conventional dosage forms, such as tablets and capsules. See page 6, lines 27-34.

Prilling is a process of forming particulates by the solidification of spray droplets of a molten composition. For pharmaceuticals, the process can be used to make particles having a diameter of about 100 to 1500 microns. See Kjaergaard et al., page 1.

One of ordinary skill in the art at the time of the invention would have recognized that by forming particles of the melt composition of Koretke et al. would increase the surface area of the composition, thereby improving the aqueous solubility of the composition in the gut after oral administration. In the instant case, absent evidence to the contrary, it would be expected that a unit dosage formulation (e.g., capsule or tablet) of a tacrolimus composition suggested by Koretke et al., in view of Kelm et al., would naturally meet the dissolution requirements of the instant claims. Additionally, one would expect, absent evidence to the contrary, that the tacrolimus composition would have a similar bioequivalence to the formulation of the instant methods (instant Claims 42-44).

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of

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ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. Claims 1, 3-10, 16-20, 22-29, 31-34, 36-44 and 51-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Patel et al. (U.S. Patent Application Pub. No. 2003/0180352 A1; previously cited), in view of Lee et al. (U.S. Patent No. 6,168,806 B1).

Patel et al. teach a solid dosage formulation comprising tacrolimus, PEG-24 cholesterol ether (SOLULAN C-24), distilled monoglycerides, and deoxycholic acid, coated on nonpareil seed having a diameter of about 400 to 500 μm . See page 41, paragraph 425. The concentration of tacrolimus in the formulation is 2 % (w/w). Distilled monoglycerides are an oily hydrophobic material with a melting point $>60^{\circ}\text{C}$. The reference teaches the formulation may also "include additional additive, excipients, and other components for the purpose of facilitating the processes involving the preparation of the composition or the pharmaceutical dosage form, as described [in the reference and] as is well-known to those skilled in the art". See page 41, paragraph 417. Patel et al. further disclose a wide variety of active ingredients (including tacrolimus) which may be dispersed in a solid carrier which comprises *inter alia* hydrophilic surfactants, including polyethylene glycol 6000 (PEG 6000). See Abstract; page 6, paragraph 76; page 9, paragraph 108 and page 43, paragraph 436. Patel et al. teach the compositions can be used for improved delivery of active ingredients. Figures 1-3 of the disclosure demonstrate improved release rates of various agents (as compared to commercial products or pure bulk drug) formulated by the methods taught

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by Patel et al. The reference discloses the "active agent can be solubilized, dispersed, or partially solubilized and dispersed" in an encapsulation coat. See page 4, paragraph 55. Patel et al. teach poloxamers, including poloxamer 188 among the most preferred surfactants for the disclosed formulations. See page 21, paragraph 183; page 23, paragraph 201. The hydrophilic surfactants utilized can be a single surfactant of a mixture of surfactants. See page 13, paragraph 144. With respect to claimed concentration ranges of the surfactants (i.e., polyethylene glycols and poloxamers) in the instant methods, it is not inventive to discover the optimum or workable ranges by routine experimentation when general conditions of a claim are disclosed in the prior art. See *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233,235 (CCPA 1955) and MPEP 2144.05(11). Patel et al. teach the formulations may include additives, including binders, fillers, flavorants, preservatives, antioxidants, bufferants, and disintegrants. See pages 27-28, paragraphs 236-260. Specific additives include, magnesium aluminum silicate, fumed silica (silicon dioxide), ethyl cellulose, cellulose acetate, cellulose nitrate, GELUCIRE 62/05, GELUCIRE 44/14, GELUCIRE 50/13, cellulose acetate phthalate (a water-miscible polymer with pH-dependent water solubility, utilized in enteric coatings). See pages 25-26, paragraph 216; page 27, paragraphs 237 and 242; page 28, paragraphs 259-260; and page 30, paragraph 280. The reference to Patel et al. further teaches a pharmaceutical composition in the form of a solid carrier wherein the solid carrier is prepared by a process without the need of introducing organic solvents. See page 2, paragraph 24 and page 45, claim 27.

Although Patel et al. disclose solid pharmaceutical compositions comprising tacrolimus on a solid carrier, and compositions comprising other water insoluble agents with poloxamers (e.g., poloxamer 188) or polyethylene glycols on solid carriers, the reference does not explicitly disclose a solid composition comprising tacrolimus, poloxamer and PEG in a single formulation.

Lee et al. disclose fast-release compositions comprising, *inter alia*, nifedipine (a water insoluble pharmaceutical agent), poloxamer 188, and PEG on a solid particulate carrier. See Abstract and Example 5. It would have been obvious to one of ordinary skill in the art at the time of the invention to formulate a tacrolimus composition as described by Patel et al., using the instantly claimed composition components disclosed by Patel et al. and exemplified by Lee et al, to, for example, improve the release profile of formulations of tacrolimus. Such would have been obvious because a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

In the instant case, absent evidence to the contrary, it would be expected that the release rates of tacrolimus from the formulation suggested by Patel et al., in view of Lee et al. would be the same as those recited by instant Claims 8-10 and 42-44. Additionally, one would expect, absent evidence to the contrary, that the tacrolimus formulation suggested by the references would have a similar bioequivalence to the formulation of the instant methods.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

14. Claims 1, 3-10, 16-20, 22-29, 31-34, 36-44 and 51-57 are rejected.
15. No claims are allowed.
16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to GREGG POLANSKY whose telephone number is (571)272-9070. The examiner can normally be reached on Mon-Thur 9:30 A.M. - 7:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gregg Polansky/
Examiner, Art Unit 1614

/James D Anderson/
Primary Examiner, Art Unit 1614